Validation of the IASLC/ATS/ERS Lung Adenocarcinoma Classification for Prognosis and Association with *EGFR* and *KRAS* Gene Mutations

Analysis of 440 Japanese Patients

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Introduction: This study aimed to validate the utility of the new histological classification proposed by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) for identifying the prognostic subtypes of adenocarcinomas in Japanese patients; correlations between the classification and the presence of *EGFR* or *KRAS* mutation status were also investigated.

Methods: We retrospectively reviewed 440 patients with lung adenocarcinoma,who underwent resection. The tumors were classified according to the IASLC/ATS/ERS classification. *EGFR* and *KRAS* mutations were detected using the established methods.

Results: Five-year disease-free survival rates were: 100% for adenocarcinoma in situ (n = 20) and minimally invasive adenocarcinoma (n = 33), 93.8% for lepidic-predominant adenocarcinoma (n = 36), 88.8% for invasive mucinous adenocarcinoma (n = 10), 66.7% for papillary-predominant adenocarcinoma (n = 179), 69.7% for acinar-predominant adenocarcinoma (n = 61), 43.3% for solid-predominant adencoarcinoma (n = 78), and 0% for micropapillary-predominant adenocarcinoma (n = 19). Multivariate analysis revealed that the new classification was an independent predictor of disease-free survival. *EGFR* and *KRAS* mutations were detected in 90 cases (53.9%) and 21 cases (13.3%), respectively; *EGFR* mutations were significantly associated with adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic- and papillary-predominant adenocarcinoma, and *KRAS* mutations adenocarcinomas with mucinous tumor subtypes.

Conclusions: We found that the IASLC/ATS/ERS classification identified prognostic histologic subtypes of lung adenocarcinomas among Japanese patients. Histologic subtyping and molecular testing for *EGFR* and *KRAS* mutations can help predict patient prognosis and select those who require adjuvant chemotherapy.

Key Words: Lung adenocarcinoma, Classification, EGFR, KRAS, Prognosis.

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Lung adenocarcinoma is the most common histologic type of primary lung cancer[1,2] and it is a heterogeneous tumor from every perspective, including the molecular, clinical, radiological, surgical, and pathological aspects.[3] Despite the discovery that *EGFR* mutation is a marker responsive to tyrosine kinase inhibitors (TKIs) and is associated with improved progression-free survival in patients with advanced lung adenocarcinoma,[4–7] the 2004 World Health Organization (WHO) histologic subclassification of resected lung adenocarcinomas has contained great challenges.[2] In this context, the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS), have proposed a new subclassification of lung adenocarcinomas.[8] Recently, in a surgical series among North American patients, we reported that the newly proposed classification of lung adenocarcinoma correlated with patient outcome.[9] A growing number of publications from Australia, Germany, and South America have validated the new subclassification,[10–12] However, there are only few reports of this type of validation for the Asian population.[13]

Many studies have shown the prevalence and specificity of molecular alterations in lung adenocarcinomas. A helpful summary was recently published, describing some of these alterations, specifically, the recognized association between the frequency of molecular alterations, including *EGFR* and *KRAS* mutations, and histologic subtypes.[8] *EGFR* mutations, found in

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approximately 30% of lung adenocarcinomas, are significantly associated with nonmucinous adenocarcinomas with a lepidic component (formerly nonmucinous bronchioloalveolar carcinoma [BAC]) and invasive carcinoma with a lepidic component, though *EGFR* mutations can also be observed in tumors with components of papillary and micropapillary histologic subtypes.[14–20] However, *KRAS* mutation status, present in approximately 10% of lung adenocarcinomas, has been shown to be significantly associated with solid and invasive mucinous adenocarcinoma subtypes,[15,21] but not in all studies.[16] Herein, whether differences in genetic alterations in lung adenocarcinomas correlate with histologic subtypes remains controversial.

The aim of the present study was to validate whether or not the proposed IASLC/ATS/ERS classification of lung adenocarcinomas correlates with patient outcomes in a surgical series of Japanese patients. In addition, we also investigated the correlation between the proposed IASLC/ATS/ERS classification of lung adenocarcinomas and *EGFR* and *KRAS* mutation status.

PATIENTS AND METHODS

Patients

Between January 2001 and December 2009, 595 consecutive patients with lung adenocarcinomas underwent pulmonary resection at Kyoto University Hospital, Japan. The patients were excluded from the present evaluation if they had multiple primary lung cancers, underwent chemo- or radiotherapy before surgery, underwent incomplete resection, or had incomplete follow-up data based on the clinical data retrieved from the thoracic surgical database. As a result, the present histological investigation included 440 lung adenocarcinomas, which met the 2004 WHO criteria for primary lung adenocarcinoma.[2] Tumor staging was performed according to the 7th edition of the tumor, node, metastasis classification of the International Union Against Cancer.[22] This project was approved by the institute's ethics committee.

Histologic Evaluation

All resected specimens were formalin-fixed, sectioned, and stained with hematoxylin and eosin, in the conventional manner. Small tumors (≤2 cm) were sampled histologically in entirety. As needed, mucin stains were performed to evaluate for the presence of mucin, and elastic stains were performed to evaluate for the presence of pleural or vessel invasions. All the histological slides were reviewed by two pathologists (AY, SS) who were blinded to patient outcomes. Because interobserver discrepancy was diminished before the review was started, both pathologists read the previous articles to determine the representative patterns of lung adenocarcinoma (lepidic, papillary, micorpapillary, acinar, and solid) and discussed their validity.[8,9,16] Thereafter, they evaluated for the extent of the representative component of lung adenocarcinoma and individually determined the predominant histologic pattern. For controversial cases, the slides were jointly reviewed under a multiheaded microscope and consensus assessment was determined. The average number of tumor slides reviewed from each case was 3.4 (range, 1–33).

All cases were histologically classified according to the 2004 WHO classification of lung adenocarcinomas.[2] Thereafter, each tumor was reviewed using comprehensive histologic subtyping, recording the percentage in 5% increments for each histologic component (Fig. 1), according to previous methods.[9,16] Subsequently, each tumor was classified according to the predominant histologic subtype or variant in each case, according to the IASLC/ATS/ERS classification scheme.[8] Tumors were classified as adenocarcinomas in situ (AIS), minimally invasive adenocarcinomas (MIA), and invasive adenocarcinomas, which were divided into lepidic-predominant (Lepidic), papillary-predominant (Pap), acinar-predominant (Aci), micropapillary-predominant (MP), solid-predominant (Solid), invasive mucinous adenocarcinoma

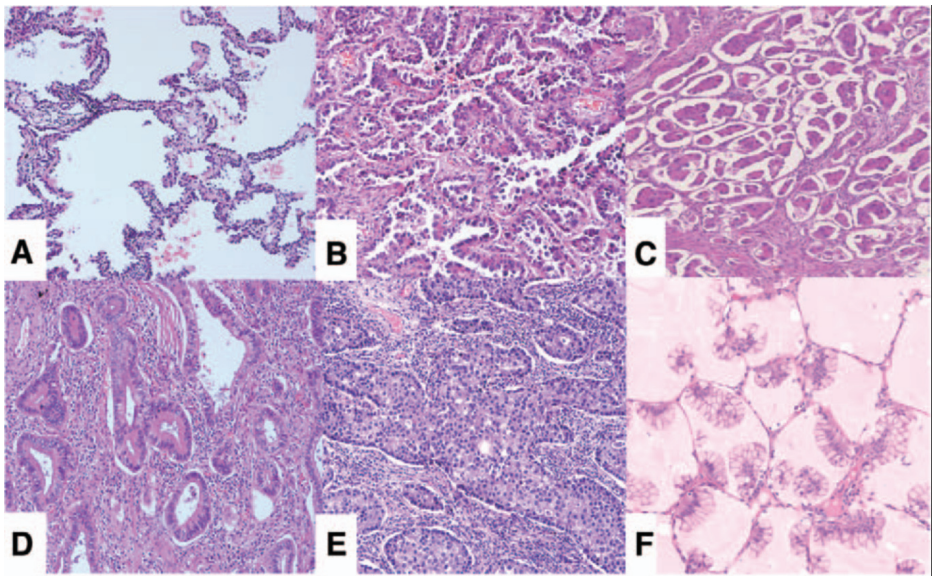

FIGURE 1. Representative histologic pattern of lung adenocarcinoma (hematoxylin and eosin stains). *A*, Nonmucinous lepidic pattern; this area shows the lepidic growth pattern, composed of nonmucinous pneumocyte-like cells. *B*, Papillary pattern; this area shows the papillary configuration of the tumor gland. *C*, Micropapillary pattern; this area shows glandular cells growing in small papillary tufts lacking fibrovascular cores within retracted connective tissue spaceii. *D*, Acinar pattern; this area shows a glandular structure, composed of round- to oval-shaped glands with desmoplastic reaction. *E*, Solid pattern; this area shows solid sheets of tumor cells. *F*, Mucinous lepidic pattern; this area shows the lepidic growth pattern, composed of goblet-cell like cells with mucin.

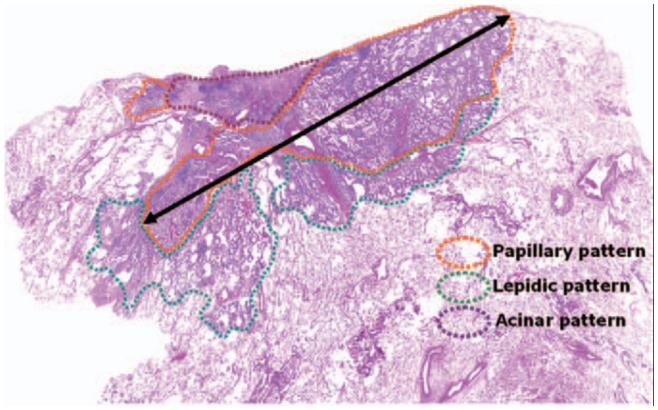

FIGURE 2. This scheme shows how the invasive area in lung adenocarcinoma is measured. The central area of the tumor shows, basically, a papillary pattern; the lepidic pattern and acinar pattern are seen in the peripheral area of this tumor. The invasive area was measured in a straight line across the largest diameter.

(IMA, formerly mucinous or mixed BAC), and others (including colloid adenocarcinoma and fetal adenocarcinoma). Cases showing signet-ring cells and clear cell features were found in eight tumors and 17 tumors, respectively. Most of these cases were included as a component of the solid subtype. Data for these cases were recorded, but they were not considered as a specific subtype.[23,24] The predominant pattern was defined as the pattern showing the greatest percentage, not necessarily 50% or greater.[8]

The total tumor size was grossly determined and recorded, whereas the invasive size was defined by measuring only the histologic subtype, not the lepidic growth pattern as previously described (Fig. 2).[8,9] The size of invasion for each case was categorized using the four groups reported by Suzuki et al.[25]: noninvasion group, 1 to 5 mm invasion group, 6 to 15 mm invasion group, and more than 16 mm invasion group.

Several histologic factors, reported as significant prognostic factors for lung adenocarcinomas, were also investigated. Lymphatic and vascular invasions were deemed to be positive when tumor cells were recognized in the lymphatic lumen or blood vessel, respectively. Visceral pleural invasion (VPI) was considered to be positive when tumor cells extended beyond the elastic layer of the pleura, as determined by elastic staining. VPI was classified as PL0, PL1, PL2, and PL3, according to the criteria established by International Union Against Cancer, 7th edition.[22] Tumor grade (well, moderately, and poorly differentiated) was assessed according to the 2004 WHO criteria.[2]

Somatic *EGFR* and *KRAS* Mutations

EGFR and *KRAS* gene mutations were detected by previously described methods.[19,26] In brief, a section from each tumor was frozen immediately after resection. To confirm that the section included carcinoma cells, a part of each tumor tissue was formalin-fixed, paraffin-embedded, sectioned, and observed microscopically. Then, a polymerase chain reaction single-strand conformational polymorphism protocol was used to detect mutations within exons 18, 19, 20, and 21 of the *EGFR* gene. For screening mutations of the *KRAS* gene, the mutagenic polymerase chain reaction restriction enzyme fragment length polymorphism method was used, as described in a previous study.[27] We sought only codon 12 mutations because only mutations in codon 12, and not codon13, of the *KRAS* gene were detected in the report.

Statistics

The impact of the following factors on the overall survival (OS) and disease-free survival (DFS) rates were evaluated: sex, age, smoking status, surgery type, tumor size, pathological stage, tumor grade, lymphatic invasion, vascular invasion, pleural invasion, *EGFR* status, *KRAS* status, and size of invasion. These clinicopathological factors were used in univariate and multivariate analyses to determine whether they had a significant effect on OS and DFS. The survival rates were calculated using the Kaplan–Meier method, and the differences were analyzed by means of the log-rank test. The multivariate analysis was performed by means of the Cox's proportional hazards model. Fisher's exact tests and χ^2 tests were used with categorical data. All statistical tests were two-sided and used a 5% level of significance. Statistical analysis was conducted using JMP version 8.0 (SAS Institute, Cary, NC).

RESULTS

Clinicopathologic Characteristics

The clinicopathologic characteristics of the patients and tumors evaluated in this study are summarized in Table 1. The patients were nearly evenly divided between the sexes (227 men [51.6%], and 213 women [48.4%]), with a mean age of 65.4 years (range, 23–86 years). Of the 425 patients with a known smoking status, 190 patients (44.7%) had never smoked, 135 patients (31.7%) were former smokers, and 100 patients (23.5%) were current smokers, with an average smoking index of 55.9 ± 4.1 pack-years. The surgical procedure employed in 14 patients (3.2%) was partial resection, in 79 (17.9%) it was segmentectomy, in 343 (80.0%) it was lobectomy, and in four (0.9%) it was pneumonectomy.

The mean tumor size was 24.3 ± 13.1 mm (range, 4–92 mm). The most common tumor size observed was less than or equal to 20 mm in diameter ($n = 214$; 48.6%), followed by tumors between 21 mm and 30 mm in diameter ($n = 118$; 26.8%), 31 to 50 mm in diameter ($n = 92$; 20.9%), and more than 51 mm in diameter ($n = 16$; 3.6%). Of the tumors with a diameter of 20 mm or lesser, only 18 did not indicate invasion, whereas 40 tumors had 1 to 5 mm invasions, 116 tumors had 6 to 15 mm invasions, and 39 tumors had more than 16 mm invasions; of the tumors between 21 mm and 30 mm in diameter, two tumors did not indicate invasions and four tumors had invasions of 1 to 5 mm. Among the tumors that had diameters of more than 31 mm, there were none without invasions or with less than 5 mm invasions.

The pathologic stage was IA in 255 patients (58.0%), IB in 80 patients (18.2%), IIA in 43 patients (9.8%), IIB in 11 patients (2.5%), and IIIA in 51 patients (11.6%). Tumor

TABLE 1. Clinicopathological Characteristics and Five-Year Survival Rate

		n	%	5-Yr Survival Rate (%)	OS (*p*)	DFS (*p*)
Sex	Male	227	51.6	63.1	0.001	0.078
	Female	213	48.4	81.3		
Age, (yrs)	<65	212	48.2	78.6	0.036	0.085
	>66	228	51.8	65.7		
Smoking status	Never	190	44.7	83.6	<0.001	0.068
	Former	135	31.7	67.3		
	Current	100	23.5	54.8		
Surgery type	Pneumonectomy	4	0.9	0	0.001	<0.001
	Lobectomy	343	80	72		
	Segmentectomy	79	17.9	79.7		
	Partial resection	14	3.2	58.4		
Tumor size (mm)	≤20mm	214	48.6	83	<0.001	<0.001
	21–30mm	118	26.8	65.8		
	31–50mm	92	20.9	65.4		
	≥51 mm	16	3.6	30.5		
Stage	IA	255	58	92.7	<0.001	<0.001
	IB	80	18.2	74.5		
	IIA	43	9.8	43.7		
	IIB	11	2.5	75		
	IIIA	51	11.6	21.4		
Tumor grade	Well differentiated	108	24.5	100	<0.001	<0.001
	Moderately differentiated	158	35.9	80.1		
	Poorly differentiated	174	39.5	51		
Lymphatic invasion	Present	74	16.8	45.2	<0.001	<0.001
	Absent	366	83.1	77.7		
Vascular invasion	Present	112	25.4	43.8	<0.001	<0.001
	Absent	328	74.5	82.6		
Pleural invasion	PL0	340	77.2	78.4	<0.001	<0.001
	PL1	53	12	62.1		
	PL2	33	7.5	52.3		
	PL3	14	3.1	0		
EGFR	Mutated	90	53.9	86.7	0.015	0.073
	Wild	77	46.1	67.6		
KRAS	Mutated	21	13.3	70.1	0.349	0.732
	Wild	137	86.7	69.9		
Size of invasion	Noninvasive	20	4.5	100	<0.001	<0.001
	1-5mm	44	10	100		
	6-15 mm	140	31.8	78.9		
	≥16 mm	236	53.6	59.7		

grades were classified as well, moderately, and poorly differentiated in 108 (24.5%), 158 (35.9%), and 174 (39.5%) of the cases, respectively. Lymphatic and vascular invasions were observed in 72 (16.4%) and 112 (25.4%) of the cases, respectively. VPI (PL1, PL2, or PL3) was observed in 100 cases (22.8%). The 2004 WHO classification and the IASLC/ATS/ERS classification of lung adenocarcinoma

The proportion of histologic subtypes of lung adenocarcinoma according to the 2004 WHO classification and the IALSC/ATS/ERS is summarized in Table 2. According to the 2004 WHO classification, 88.4% of the cases were classified as mixed subtypes, with 20 tumors classified as BAC. Of the 20 BAC tumors, only one was a mucinous BAC (100% BAC growth pattern tumor composed of mucinous tumor cells). Thus, according to the IASLC/ATS/ERS classification, 19 tumors (4.5%) and one tumor (0.1%) were classified as nonmucinous AIS and mucinous AIS, respectively. There were 332 tumors that were categorized in the less than or equal to 3 cm group. Among them, 64 tumors without invasion or with invasions of 5 mm or lesser were identified. After elimination of 20 AISs, the remaining 44 cases comprised 36 tumors with the Lepidic pattern and eight tumors with the *other* pattern. Within the group of 36 tumors, there were two cases with pleural invasion and one

case with necrosis. Hence 33 MIAs, which included 31 nonmucinous and two mucinous MIAs, were identified.

The most common histologic subtype among the invasive adenocarcinomas was Pap (n = 179; 40.7%), followed by Solid (n = 78; 17.7%), Aci (n = 61; 13.8%), Lepidic (n = 36; 8.1%), MP (n = 19; 4.3%), IMA (n = 10; 2.2%), and others (n = 4; 0.9%). The others included three colloid adenocarcinomas and one fetal adenocarcinoma. No enteric adenocarcinomas were identified in this study.

EGFR and *KRAS* Mutation Status

Of the 440 cases, 167 cases were examined for *EGFR* mutations and 158 cases were examined for *KRAS* mutations, and the *EGFR* and *KRAS* mutations were mutually exclusive. *EGFR* mutations were detected in 90 cases (53.9%) and mutations within codon 12 of *KRAS* were observed in 21 cases (13.3%). The cases with *EGFR* mutations were significantly associated with female patients, patients who never smoked, and patients with small tumors ($p < 0.001$, $p < 0.001$, $p = 0.027$). However, *KRAS* mutations were significantly associated with former and current smokers ($p = 0.034$). (Table 3)

Figure 3 shows the correlations between the frequency of *EGFR* or *KRAS* mutations and the proposed IALSC/ATS/ERS histologic classification. *EGFR* mutations were associated with a high frequency of AIS, MIA, Lepidic, and Pap subtypes (frequency: 85.7% AIS, 83.3% MIA, 71.4% Lepidic, and 68.5% Pap), followed by Aci (38.4%) and MP (40.1%) subtypes, whereas they were uncommon in Solid subtype tumors (14.3%) (Fig. 3A). Moreover, *EGFR* mutations were not detected in mucinous subtype tumors, including mucinous MIAs and IMAs. However, *KRAS* mutations were detected more often in Aci (23.1%) and Solid (25.0%) subtypes, followed by the MIA (8.3%), and Pap (4.5%) subtypes (Fig. 3B). No *KRAS* mutations were observed in AIS or Lepidic subtypes, whereas all IMAs (n = 4) had *KRAS* mutations.

The IASLC/ATS/ERS classification was also examined to determine whether specific tumor features (nonmucinous lepidic, mucinous lepidic, papillary, acinar, solid, micropapillary) reflected *EGFR* and *KRAS* mutation status (data not shown). *EGFR* mutations were more frequently found in the adenocarcinomas with nonmucinous lepidic ($p < 0.001$) and papillary ($p < 0.001$) components than in tumors without those components. Conversely, *EGFR* mutations were less frequently found in adenocarcinomas with either mucinous lepidic ($p < 0.001$) or solid ($p < 0.001$) components than in tumors without those components. The most common *EGFR* mutation was in-frame deletions in exon 19 (48 of 90, 53.3%), and the second common mutation was missense mutation (L858R) in exon 21 (36 of 90, 40.0%). The correlation between the two major *EGFR* mutations (in-frame deletions in exon19 and missense mutations in exon 21) and the presence of the six major characteristics, as defined by the IASLC/ATS/ERS classification, were not distinct. However, *KRAS* mutations were less frequently found in adenocarcinomas with

TABLE 2. Adenocarcinoma Subtypes by IASLC/ATS/ERS and 2004 WHO Classifications

		n	%
IASLC/ATS/ERS classification	AIS(nonmucinous/mucinous)	20 (19/1)	4.5
	MIA(nonmucinous/mucinous)	33 (31/2)	7.5
	Lepidic	36	8.1
	Aci	61	13.8
	Pap	179	40.7
	Solid	78	17.7
	MP	19	4.3
	IMA	10	2.2
	Others	4	0.9
2004 WHO classification	Mixed subtype	389	88.4
	BAC(nonmucinous/mucinous)	20 (19/1)	4.5
	Acinar	2	0.5
	Papillary	7	1.6
	Solid with mucin	21	4.8
	Others	1	0.2

IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society; WHO, World Health Organization; MP, micropapillary-predominant; IMA, invasive mucinous adenocarcinoma; BAC, bronchioloalveolar carcinoma; Pap, papillary-predominant; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma

TABLE 3. Relationship between Clinicopathological Characteristics and EGFR Mutations/KRAS Mutations

		EGFR Mutation			*EGFR* Mutation Detail					KRAS Mutation		
		Mutated	Wild	p^a	Exon18	Exon19	Exon20	Exon21	p^b	Mutated	Wild	p^a
Total		90	77		3	48	3	36		21	137	
Age, (yr)	<65	42	31	0.405	1	26	2	13	0.1	11	57	0.353
	>66	48	46		2	22	1	23		10	80	
Sex	Male	29	45	<0.001	1	18	1	9	0.224	12	59	0.227
	Female	61	32		2	30	2	27		9	78	
Smoking status	Never	59	22	<0.001	1	31	2	25	0.736	6	73	0.034
	Former/current	30	51		2	16	1	11		15	64	
Tumor size	<30mm	74	52	0.027	3	38	3	30	0.630	15	106	0.549
	>31mm	16	25		0	10	0	6		6	31	

[a]By χ^2 test or Fisher's exact test.
[b]Comparing difference between Exon19 and Exon21 by χ^2 test or Fisher's exact test.

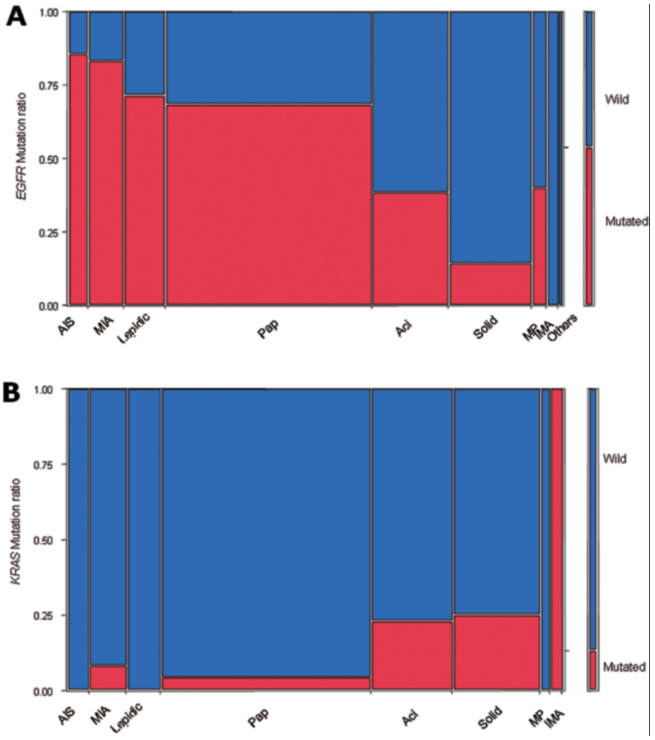

FIGURE 3. Correlations between frequencies of *EGFR* or *KRAS* mutations and the histologic subtype of the adenocarcinomas, based on the IASLC/ATS/ERS classification. *A*, *y* axis indicates the frequency of *EGFR*-mutated cases and the *x* axis indicates frequency of lung adenocarcinoma subtypes, based on the new IASLC/ATS/ERS classification; (*B*), *y* axis indicates the frequency of *KRAS*-mutated cases and the *x* axis indicates the frequency of lung adenocarcinoma subtypes, based on the IASLC/ATS/ERS classification. AIS, adenocarcinoma in situ, MIA, minimally invasive adenocarcinoma, Lepidic, lepidic predominant adenocarcinoma, Aci, acinar predominant adenocarcinoma, Pap, papillary predominant adenocarcinoma, Solid, solid predominant adenocarcinoma, MP, micropapillary predominant adenocarcinoma, IMA, invasive mucinous adenocarcinoma; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society.

nonmucinous lepidic component ($p < 0.001$) than in tumors without this characteristic and were also more frequently found in adenocarcinomas with the mucinous lepidic component ($p < 0.001$) than in those without it.

Survival Analysis

Sixty-five patients (14.8%) died as a result of their disease and another seven (1.6%) died of other or unknown causes during the study follow-up period. The mean clinical follow-up period was 38.3 months (range, 0.4–103 months). Of the 368 patients (83.6%) alive at the time of the analysis, 40 (9.0%) experienced recurrent disease and 328 (74.5%) had no evidence of disease. Therefore, a total of 105 patients either died as a result of their cancer or experienced postsurgical recurrence and were included in the DFS analysis.

Figure 4A shows the DFS curves, according to IASLC/ATS/ERS lung adenocarcinoma subtype. AIS and MIA subtypes were associated with patients with significantly better prognoses and a 100% DFS at 5 years. This was followed by patients with the Lepidic subtype (5-year DFS rate = 93.8%), and the IMA subtype (5-year DFS rate = 88.8%). Solid and MP subtypes showed the worst prognoses, with a 43.3% DFS at 5 years and a 0% DFS at 3 years, respectively. Aci (5-year DFS rate = 69.7%) and Pap (5-year DFS rate = 66.7%) were identified as the intermediate survival group between AIS/MIA/Lepidic/IMA subtypes and Solid/MP subtypes. Figure 4B shows the overall survival curves, grouped by the IASLC/ATS/ERS classification of lung adenocarcinomas. None of the patients with AIS and MIA subtypes died within the follow-up period. The patients with the lepidic subtype also showed significantly better prognoses with a 5-year OS rate of 100%, followed by those with the IMA (5-year OS rate = 88.8%), Aci (5-year OS rate = 81.2%), and Pap (5-year OS rate = 74.7%) subtypes. Solid and MP subtypes were associated with patients with the worst prognoses, with a 39.1% OS rate at 5 years and a 42.0% OS rate at 3 years (the follow-up period did not reach 5 years), respectively. However, the OS curves of the two subtypes were not clearly separated, compared with their DFS curves.

Table 1 also shows the results of the univariate analyses of the clinicopathologic factors evaluated in this study. The 5-year survival rates for the stage IA, IB, IIA, IIB, and IIIA groups were 92.7%, 74.5%, 43.7%, 75.0%, and 21.4%, respectively, and the differences were statistically significant ($p < 0.001$). Male, aged patients (≤65 years versus > 66 years), and former and current smokers (never versus former/current) correlated significantly with worse OS ($p = 0.001$, $p = 0.036$, and $p < 0.001$, respectively), although, these were not significant for DFS. As for the histological parameters, tumor grade by the 2004 WHO classification (well differentiated versus moderately differentiated versus poorly differentiated), lymphatic invasion (present versus absent), vascular invasion (present versus absent), and VPI (PL0 versus PL1/2/3) were also significant predictors of OS ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). In addition, invasion size was also related to DFS; the noninvasion and 1 to 5 mm invasion groups showed significantly better prognoses with 100% DFS at 5 years, compared with the 6 to 15 mm invasion group (5-year DFS rate = 78.9%). The group with more than 16-mm invasion showed the worst prognosis with a 51.7% DFS rate at 5 years.

The presence of specific gene mutations also seemed to impact OS rates. Patients with tumors having *EGFR* mutations showed significantly better prognosis, with an 86.7% OS rate at 5 years compared with patients with tumors lacking the *EGFR* mutations (5-year OS rate = 67.6%). However, the difference in DFS rates between these groups did not reach statistically significant levels. The differences in both OS and DFS were also not statistically significant between patients with mutated *KRAS* genes and those with the wild type *KRAS* genes.

On the basis of the results of these univariate analyses, multivariate analyses were performed using the Cox proportional hazards model. As shown in Table 4, the

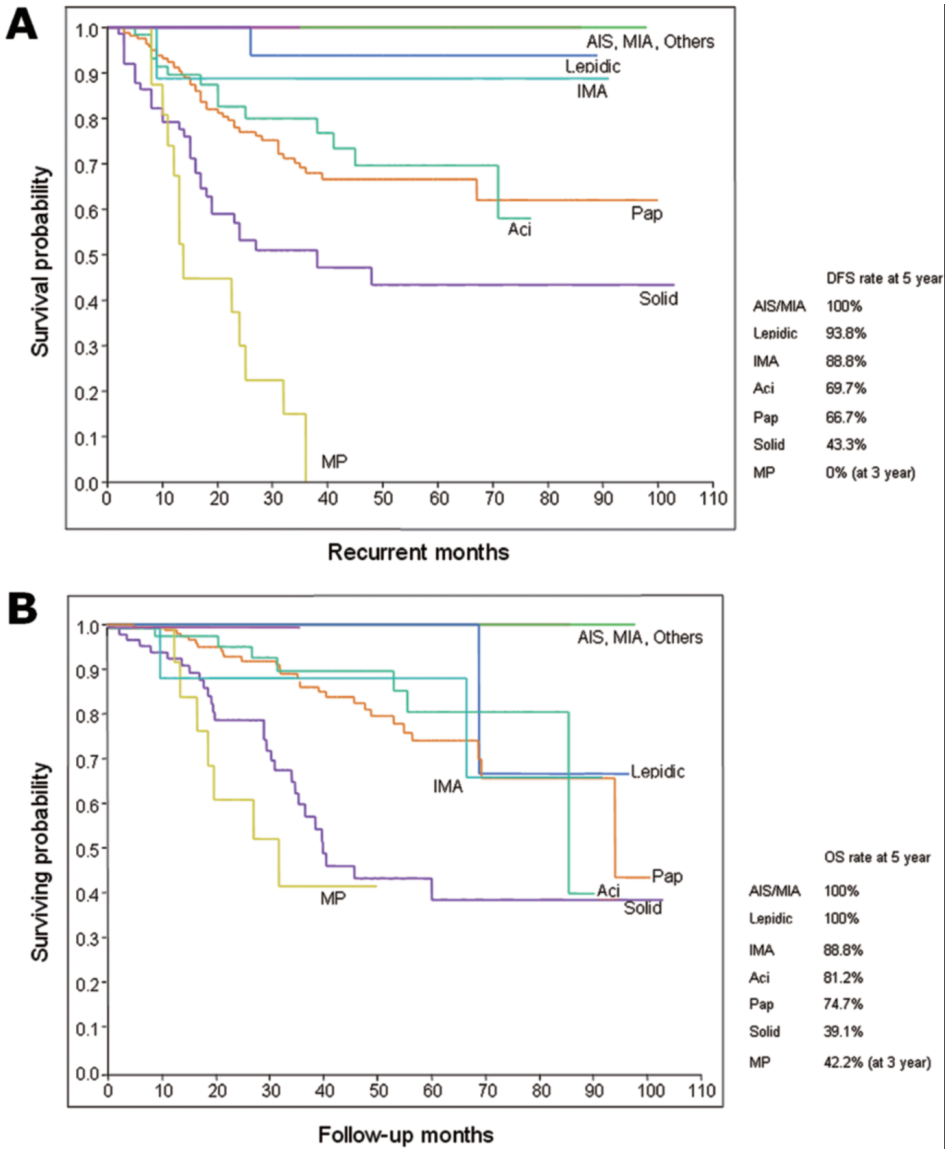

FIGURE 4. *A*, Disease-free survival curves and (*B*) overall survival curves, for the groups, separated by the IASLC/ATS/ERS classification of lung adenocarcinomas. AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; Lepidic, lepidic predominant adenocarcinoma; Aci, acinar predominant adenocarcinoma; Pap, papillary predominant adenocarcinoma; Solid, solid predominant adenocarcinoma; MP, micropapillary predominant adenocarcinoma; IMA, invasive mucinous adenocarcinoma; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society.

multivariate analyses indicated that pathological stage, size of invasion, and tumor grade by the IASLC/ATS/ERS classification remained significantly associated with DFS; patients with stage II or III tumors indicated an increased risk for recurrence, compared with those with stage I tumors (hazard ratio [HR] = 4.23, 95% confidence interval [CI]: 2.76–6.55, $p < 0.001$). Similarly, tumors with invasions of more than 6 mm also indicated an increased risk of recurrence, compared with tumors without invasion or with invasions of 5 mm or lesser (HR = 2.00E+5, 95% CI: 2.85–7.2E+165, $p = 0.001$); the high-grade group (Solid/MP/Colloid) also indicated an increased risk of recurrence, compared with the low- and intermediate-grade groups (AIS/MIA/Lepidic/Aci/Pap/IMA), based on the IASLC/ATS/ERS classification. Moreover, the pathological stage and the IASLC/ATS/ERS classification remained significantly associated with OS; patients with stage II or III tumors had increased risks of overall death, compared with patients with stage I tumors (HR = 4.82, 95% CI: 2.86–8.33, $p < 0.001$). Moreover, the high-grade group had an increased risk of overall death, compared with the low- and intermediate-grade groups, based on the IASLC/ATS/ERS classification (HR = 3.24, 95% CI: 1.79–6.01, $p < 0.001$).

DISCUSSION

In this study, the proposed IASLC/ATS/ERS histologic subtypes of lung adenocarcinomas could predict the prognosis of a patient who underwent surgical resection, and the IASLC/ATS/ERS classification would be one of the independent parameters for predicting a high risk of recurrence and incidence of death by primary lung cancer. Our results almost confirm previous studies on predominantly white patients.[9–12]

Recent advances in diagnostic imaging have enhanced the capability for early-stage diagnosis, and histopathologic studies have indicated the presence of favorable prognostic subgroups among patients with lung adenocarcinomas.

TABLE 4. Multivariate Survival Analysis for Disease-Free Survival and Overall Survival

	DFS			OS		
Parameter	**Hazard Ratio**	**95% CI**	***p***	**Hazard Ratio**	**95% CI**	***p***
Surgery type (Lob./Seg./PR vs. pneumonectomy)[a]	0.46	0.17–1.64	0.211	0.37	0.12–1.39	0.131
Stage (II/III vs. I)	4.23	2.76–6.55	<0.001	4.82	2.86–8.33	<0.001
Tumor grade by 2004 WHO classification (poorly vs. well/moderately)	1.35	0.80–2.31	0.255	0.97	0.49–1.92	0.945
Tumor size (>31 mm vs. 1–30 mm)	1.34	0.88–2.03	0.163	1.06	0.63–1.75	0.799
Lymphatic invasion (present vs. absent)	1.1	0.70–1.70	0.645	1.54	0.89–2.60	0.115
Vascular invasion (present vs. absent)	1.45	0.94–2.24	0.089	1.43	0.84–2.41	0.176
Pleural invasion (PL1, PL2, PL3 vs. PL0)	1.27	0.83–1.92	0.248	1.37	0.82–2.26	0.216
Invasion degree (>6 mm vs. 0–5 mm)	2.00E+05	2.851–7.2E+165	0.001	2.83	0.55–51.69	0.245
Tumor grade by IASLC/ATS/ERS classification (high vs. low/intermediate)[a]	1.71	1.06–2.77	0.026	3.24	1.79–6.01	<0.001

[a]IASLC/ATS/ERS classification (low-grade group: AIS/MIA, intermediate-group: Lepidic/Aci/Pap/IMA, high-grade group: Solid/MP/Colloid).

DFS, disease-free survival; OS, overall survival;CI, confidence interval; Lob, lobectomy; Seg, segmentectomy; PR, partial resection AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society; WHO, World Health Organization; Solid, solid predominant adenocarcinoma; MP, micropapillary predominant adenocarcinoma.

Noguchi et al.[28] proposed that types A and B tumors, localized BAC without and with foci of collapsed alveolar structures, were associated with excellent patient prognosis (100% 5-year survival). According to the WHO classifications, published in 1999 and 2004 and which were strongly affected by the report by Noguchi et al.,[28] BAC was strictly defined as adenocarcinoma with a pure lepidic growth pattern without stromal, vascular, or pleural invasion. Nonetheless, the term *BAC* has been broadly used, and has included AIS, MIA, and invasive adenocarcinomas with lepidic components.[9,10,16,25,29–34] In the new proposed IASLC/ATS/ERS classification, the term of *BAC* has been discontinued. At present, AIS and MIA, as per the new classification, are tumors that should have 100% 5-year DFS, if completely resected.

MIA is a new lung adenocarcinoma subtype defined as a small solitary adenocarcinoma (≤3 cm), with a predominantly lepidic pattern and invasion of 5 mm or lesser.[8] Moreover, the IASLC/ERS/ATS classification excludes tumors that invade the lymphatics, blood vessels, or pleura, and those that contain necrosis, from the MIA subtype.[8] This concept was based on only a few studies. In Suzuki's study[25] of 100 lung adenocarcinomas measuring 3 cm or lesser, they classified invasion according to the size of the fibrotic scar in the tumor. They reported 100% 5-year survival for patients with tumors in the less than or equal to 5-mm group, 72% 5-year survival for tumors in the 6- to 15-mm group, and 57% 5-year survival for those that were in the more than 15-mm group. Sakurai et al.[31] also examined 380 peripheral adenocarcinomas of less than or equal to 2-cm diameter and found that only 3.3% of the 91 patients with fibrosis less than or equal to 5 mm had recurrence and importantly, 100% were alive at 7 years. Recently, Maeshima et al.[35] reported that adenocarcinomas comprised non-BAC tumors with less than or equal to 5-mm invasive area did not exhibit recurrence in their large series. All the abovementioned studies were conducted in Japan, raising concerns that these findings may not be applicable worldwide. However, recently, some studies based in the United States have demonstrated increased survival for patients with tumors having less than or equal to 5 mm of invasion.[9,11,12,29,36] Our data with 36 MIAs confirmed that all had 100% 5-year DFS and OS, thus supporting the proposed concept and criteria by the IASLC/ATS/ERS classification.

There are very limited numbers of reports regarding the prognosis for mucinous AIS and mucinous MIA. We identified one mucinous AIS and two mucinous MIAs in this study. All these tumors were associated with 100% 5-year DFS. The mucinous AIS classification can be traced back to the original article on BAC by Noguchi et al.,[28] where two mucinous cases were included. Ichinokawa et al.[37] reported that the 5-year DFS rate and OS rate for 46 lung adenocarcinomas, predominantly composed of goblet cells, were 95.7% and 89.8%, respectively. However, we are not certain whether any of these tumors would have been classified as AIS or MIA. In this study, no pathological details were provided, but it seems that 25 tumors may have been classified as mucinous AIS and one as MIA, and they may have had a 100% 5-year DFS. Oka et al.[38] also reported that eight patients with mucinous BACs measuring less than 30 mm had a 100% 5-year OS, although pathological details were not documented. Our previous report based on an American population showed only one patient with mucinous MIA, who did not have recurrence.[9] Although more data are needed to further explore the prognostic significance of mucinous AIS and MIA, the two categories are considered good prognostic groups, similar to the nonmucinous AIS and MIA. Compared with mucinous AIS and mucinous MIA, in this study, we found that IMA had an 88.9% 5-year DFS rate. IMA is often an aggressive tumor with a multinodular, multilobar, and bilateral presentation, and can recur and be fatal even when at stage I.[36–38] However, the extent to which this subtype has malignant potential remains unclear. In the present Japanese population-based study, the DFS and OS curves for IMA were intermediate between the low-grade (AIS/MIA) and high-grade groups (Solid/MP), whereas the IMA subtype had a poor prognosis, along with the Solid and MP subtypes, in the previous American population-based study.[9] Conversely, a report from Germany by Warth et al.[11]

showed that IMA had a better prognosis than the bulk of lung adenocarcinomas. As for gene alterations, the IMA subtype has been shown to harbor none or few *EGFR* mutations, rather favoring *KRAS* mutations,[21,39,40] and are therefore, known to be resistant to EGFR-TKIs, and to have no specific treatment.[41] In the present cohort, *KRAS* mutations were more frequently seen in adenocarcinomas with mucinous lepidic components than in those without this component. In addition, all IMA tumors (4 cases tested) had *KRAS* mutations detected. To consider treatments for this subtype better, a larger cohort will need to be studied because of the very low occurrence of this subtype among the total number of patients with lung adenocarcinomas.

In the present cohort, the most predominant histologic subtype was the Pap; patients with the Pap subtype had relatively good survival rates, similar to the Aci subtype, and consistent with the results observed from American and Australian patient reports.[9,10] However, a study by Warth et al.[11] reported a worse survival rate for the Pap subtype, possibly the result of different ethnic backgrounds, geographical regions, or histologic recognition of the pattern. In addition, the use of EGFR-TKIs may also be one of the causes for these discrepancies. In the current work, the incidence of *EGFR* mutations was very high in the Pap subtype and in the AIS and MIA subtypes, which is also supported by previous reports.[14–20] In addition, these mutations were more frequently observed in adenocarcinomas with a papillary component than in those without the component. These results indicate that the use of EGFR-TKIs for patients with this subtype may influence its prognosis. Although tumors with nonmucinous lepidic components are strongly associated with *EGFR* mutations, EGFR-TKIs may have a narrow window of opportunity for use for the subtypes because most of the subtypes exhibited better prognosis. Thus, the prognosis of adenocarcinomas of the Pap subtype require further study, after adjusting for the use of EGFR-TKIs.

In the current study, we found that the Solid subtype of adenocarcinomas also had a relatively poor prognosis, which is consistent with a growing number of studies.,[9,42,4311] In addition, the MP subtype was found to have a poor outcome, in this study. The poor prognosis associated with the micropapillary pattern confirms observations of multiple previous studies and supports the addition of this new subtype to the classification scheme.[44–48] Interestingly, the 3-year DFS rate for the MP subtype was significantly worse than the 3-year DFS for the Solid subtype in the present set of data. However, the 3-year OS rates were not distinct, similar to the findings of Warth et.al.[11] The prognostic differentiation between the two subtypes might be influenced by *EGFR* status, as the frequency of *EGFR* mutations in the MP subtype was higher than in the Solid subtype tumors. Moreover, *EGFR* mutations were less frequently observed in adenocarcinomas with solid components than in those without that component, again, as found in previous reports.[16,17] Therefore, the MP subtype is speculated to easily to recur, but to be more susceptible to EGFR-TKIs in comparison with the Solid subtype tumors.

In summary, our study indicates that the new IASLC/ATS/ERS classification identifies histologic subtypes of lung adenocarcinomas with prognostic value among Japanese patients. Moreover, *EGFR* mutations were significantly identified in AIS/MIA/Lepidic/Pap subtypes. Conversely, *KRAS* mutations were frequently identified in mucinous subtypes. On the basis of these findings, we believe that histologic subtyping and molecular testing for *EGFR* and *KRAS* mutations are helpful for predicting prognosis among patients with resectable lung cancer and may be helpful in selecting patients who require adjuvant chemotherapy.

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